

Evaluation of the effect of magnesium vs. midazolam as adjunct to epidural bupivacaine in patients undergoing total knee replacement

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ABSTRACT

Background and objectives: Effective pain management is an important component of intraoperative and postsurgical care; it can prevent pain related clinical complications and improve the patient quality of life. This prospective, randomized, double-blind study was designed to evaluate analgesic efficacy of adding magnesium and midazolam to epidural bupivacaine in patients undergoing total knee replacement.

Methods: 120 patients ASA I and II, undergoing total knee replacement surgery were enrolled to receive either bupivacaine 0.5 % or bupivacaine 0.5 % plus magnesium sulphate 50 mg as an initial bolus dose followed by a continuous infusion of 10 mg/h or bupivacaine 0.5 % plus midazolam 0.05 mg/kg as intraoperative epidural analgesia. Postoperatively, all patients were equipped with a patient-controlled epidural analgesia device. Heart rate, mean arterial pressure, oxygen saturation, respiratory rate, pain assessment using a visual analogue scale (VAS), sedation score, patients' first analgesic requirement times and postoperative fentanyl consumption were recorded.

Results: The intraoperative VAS was significantly less in magnesium and midazolam groups. Whereas, in the first postoperative hour, VAS was significantly less in magnesium group. The postoperative rescue analgesia as well as the PCEA fentanyl consumption was significantly reduced in magnesium group.

Conclusion: Co-administration of epidural magnesium provides better intraoperative analgesia as well as analgesic-sparing effect on PCEA consumption without increasing the incidence of side-effects.

KEYWORDS: Epidural analgesia, Magnesium, midazolam

Introduction

The effective relief of pain is of paramount importance to anyone treating patients undergoing surgery. Not only does effective pain relief mean a smoother postoperative course with earlier discharge from hospital, but it may also reduce the onset of chronic pain syndromes¹. Regional anaesthesia is a safe, inexpensive technique, with the advantage of prolonged postoperative pain relief. Research continues concerning different techniques and drugs that could prolong the duration of regional anaesthesia and postoperative pain relief with minimal side effects¹. Magnesium is the fourth most plentiful cation in the body. It has antinociceptive effects in animal and human models of pain^{2,3}. Previous studies had proved the efficacy of intrathecally administered magnesium in prolonging intrathecal opioid analgesia without increase in its side effects. These effects have prompted the investigation of epidural magnesium as an adjuvant for postoperative analgesia⁴.

Midazolam, a water-soluble benzodiazepine, has proved epidural analgesic effect in patients with postoperative wound pain. Serum concentrations of midazolam after an epidural administration were smaller than those producing sedative effects in humans⁵.

The purpose of this study is to compare the analgesic efficacy of epidural magnesium to that of midazolam when administered

with bupivacaine in patients undergoing total knee replacement.

Methods:

After obtaining the approval of the Hospital Research & Ethical Committee and patient's informed consent, 120 ASA I and II patients of both sexes, aged 50-70 years undergoing total knee replacement surgery were enrolled in this randomised, double blinded placebo-controlled study. Those who had renal, hepatic impairment, cardiac disease, spine deformity, neuropathy, coagulopathy or receiving anticoagulants for any cause were excluded from the study.

Prior to surgery, the epidural technique as well as the visual analogue scale (VAS; 0: no pain; 10: worst pain) and the patient-controlled epidural analgesia device (PCEA) were explained to the patients.

The protocol was similar for all patients. Patients received no premedication. Heart rate (HR), mean arterial pressure (MAP) and oxygen saturation (SpO₂) were measured. Intravenous access had been established and an infusion of crystalloid commenced.

Before the induction of anaesthesia, an epidural catheter was placed at the L₃-L₄ or L₄-L₅ intervertebral space under local anaesthesia with the use of loss of resistance technique, and

correct position was confirmed by injection of lidocaine 2% (3ml) with epinephrine in concentration 1: 200 000. An epidural catheter was then inserted into the epidural space. The level to be blocked was up to T10 in a double blind fashion and using a sealed envelope technique, patients were randomly allocated to one of three equal groups to receive via epidural catheter either 50 mg magnesium sulphate (MgSO₄) in 10 ml as an initial bolus dose followed by infusion of 10 mg/h (diluted in 10 ml saline) during the surgery (Mg group) or 10 ml saline followed by infusion of saline 10 ml/h during the surgery (control group) or 0.05 mg/kg of midazolam in 10 ml saline (Midazolam group) followed by infusion of saline 10 ml/h during the surgery. All patients received epidural bupivacaine 0.5 % in a dose of 1ml/segment .

Sensory block was assessed bilaterally by using loss of temperature sensation with an ice cube. Motor block was evaluated using a modified Bromage scale ⁶ (0: no motor block, 1: inability to raise extended legs, 2: inability to flex knees, 3: inability to flex ankle joints). During the course of operation, epidural bupivacaine 0.5% was given, if required, to achieve a block above T₁₀MAP, HR, SpO₂ and respiratory rate (RR) were recorded before and after administration of the epidural medications and every 5 minutes till end of the surgery.

When surgery was complete, all patients received PCEA using a PCEA device (Infusomat[®] Space, B.Braun Space, Germany) containing fentanyl 2 µg/ml and bupivacaine 0.08% (0.8 mg/ml). The PCEA was programmed to administer a demand bolus dose of fentanyl 5 ml with no background infusion and lockout interval 20 min. The PCEA bolus volume was titrated according to analgesic effect or occurrence of side-effects. Patients' first analgesic requirement times were recorded. The time from the completion of the surgery until the time to first use of rescue medication by PCEA was defined as the time to first requirement for postoperative epidural analgesia. A resting pain score of ≤ 3 was considered as a satisfactory pain relief. If patients had inadequate analgesia, supplementary rescue analgesia with intramuscular pethidine 50 mg was available. MAP, HR, SpO₂, RR and pain assessment using VAS were recorded at 30 minutes, and then at 1, 2, 4, 8, 12, and 24 h in the postoperative period. Epidural fentanyl consumption was also recorded at the same time points. Patients were discharged to the ward when all hemodynamic variables were stable with completely resolved motor block, satisfactory pain relief, and absence of nausea and vomiting. Adverse events related with the epidural drugs (sedation, respiratory depression, nausea, vomiting, prolonged motor block) and epidural catheter were recorded throughout the 24 h study period. Sedation was assessed with a five-point Scale: 1: Alert/active, 2: Upset/wary, 3: Relaxed, 4: Drowsy, 5: Asleep. A blinded anaesthesiologist who was unaware of the drug given, performed all assessments.

The results were analyzed using SPSS version 17. The number of subjects enrolled was based on a power calculation of finding a 20% change in HR and MAP. The α -error was assumed to be 0.05 and the type II error was set at 0.20. Numerical data are presented as median and 95% CI. The groups were compared with analysis of variances (ANOVA). The VAS pain scores were analyzed by Mann-Whitney U test. Categorical data were compared using the Chi square test. *P* value of 0.05 was used as the level of significance.

Results:

The three groups were comparable in respect of age, weight, height, sex, ASA status and duration of surgery (Table 1). Patients in all groups were comparable regarding intra or postoperative MAP, HR (Figure 1,2), RR and SpO₂ during the observation period with no case of hemodynamic or respiratory instability. No difference in the quality of sensory and motor block before and during the surgery was noted between groups, and none of the patients required supplemental analgesia during surgery.

	Control	Mg	Midazolam
No of patients	40	40	40
Sex (female/male)	17/23	20/20	19/21
Age (yrs)	59.5 ± 6.1	61.1 ± 4.9	61.9 ± 3
ASA (I/II)	12/28	14/26	11/29
Weight (Kg)	69.7 ± 4.2	66.9 ± 6.7	70.1 ± 5.5
Height (cm)	165.9 ± 8.6	170.2 ± 4.5	167.2 ± 6.9
Duration of surgery (min)	144 ± 21	129 ± 30	130 ± 27
(median and 95% CI or number). No significant difference among groups			

Table 1: Demographic data and duration of surgery.

The intraoperative VAS was significantly less in magnesium and midazolam groups compared to control group after 15 and 30 minutes (Figure 3). Whereas the postoperative VAS was significantly less in the magnesium group in the first postoperative hour compared to other groups (Figure 4).

The time of request for postoperative analgesia was significantly delayed and the number of patients requesting postoperative analgesia was significantly reduced in magnesium group (Figure 5). Moreover, the pethidine rescue analgesia consumption and the total amount of postoperative fentanyl infusion were significantly reduced in magnesium group compared to other groups (Table 2) (Figure 5).

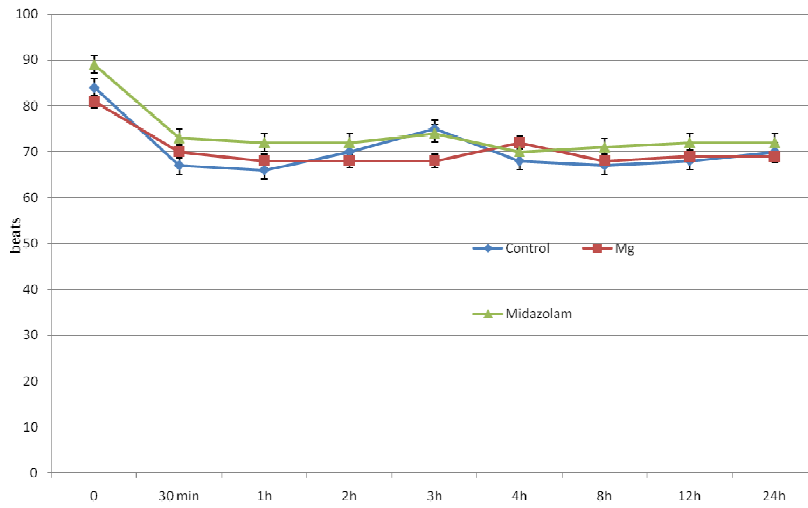


Figure 1: Heart rate changes (HR) of study groups. Data are mean±SD.

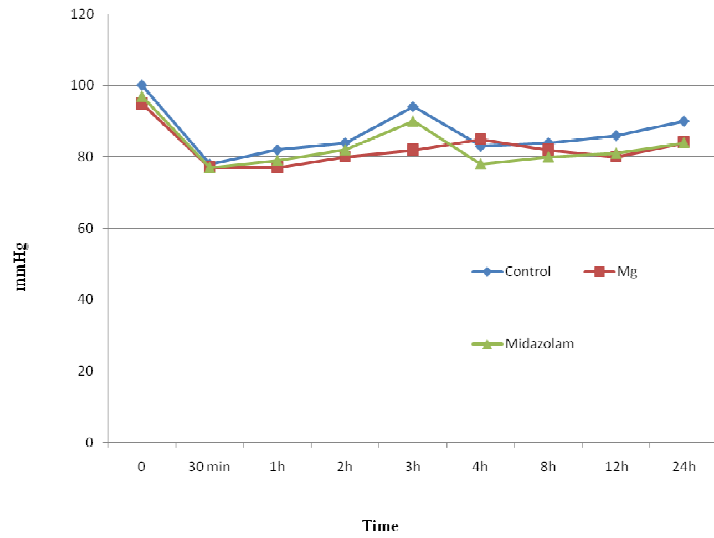


Figure 2: Mean Arterial pressure changes (MAP) of study groups. Data are mean±SD.

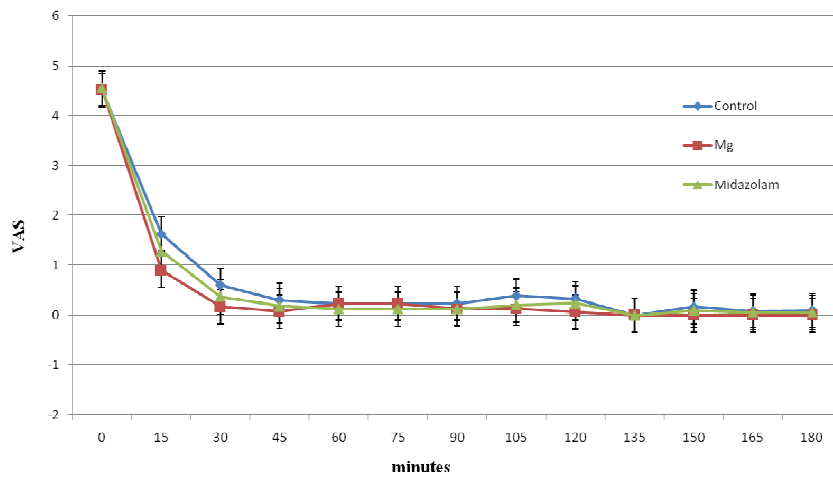


Figure 3: The intra-operative Visual analogue score of study groups. Data are mean±SD.

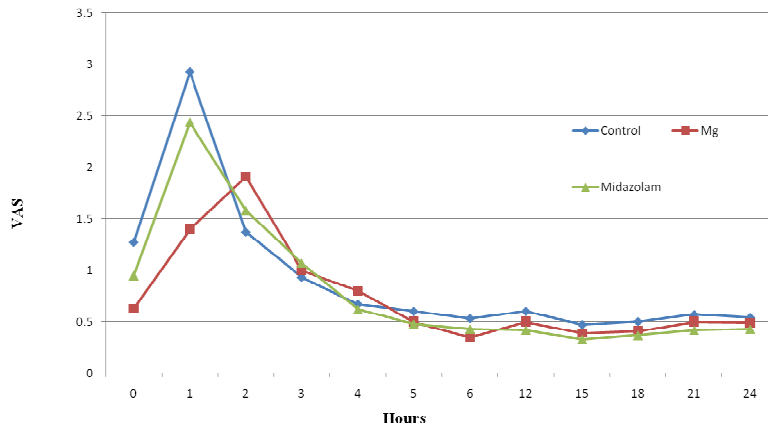


Figure 4: The post-operative Visual analogue score of study groups. Data are mean±SD.

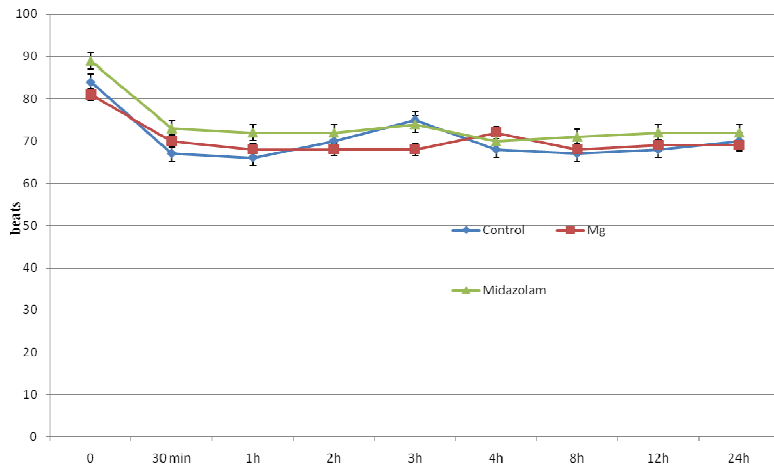


Figure 5: The number of patients and time of requesting analgesia in the first 3 postoperative hours in the study groups. Data are numbers.

	Control	Mg	Midazolam	P
Pethidine (mg)	92.38±10.91	52.56±9.67	70±9.23	0.014*
Total Fentanyl infusion (mcg)/24H	320.67±112.19	219.9±56.86	256.2±53.49	0.00*
Data are expressed as median and 95% CI. * Significant difference (P < 0.05).				

Table 2: Pethidine rescue analgesia and total fentanyl infusion over 24 hours of study groups

	Control	Mg	Midazolam	P
Sedation	0	0	2	0.068
Bradycardia	1	0	0	0.103
Nausea & Vomiting	3	1	2	0.571
Data are expressed as numbers. Significant difference (P < 0.05).				

Table 3: Incidence of sedation, bradycardia and nausea & vomiting in the study groups

No significant differences were recorded regarding the incidence of sedation or any adverse effects between groups (Table 3).

Discussion:

The efficacy of postoperative pain therapy is a major issue in the functional outcome of the surgery⁷. It was evident that epidural analgesia regardless the agent used provides better postoperative analgesia compared with parental analgesia. The addition of adjuvants to local anaesthetics in epidural analgesia gained widespread popularity as it provides a significant analgesia which allows the reduction of the amount of local anaesthetic and opioid administration for postoperative pain and thus the incidence of side effects⁹.

Our study demonstrates a significant intraoperative improvement in VAS in magnesium and midazolam groups, while in the postoperative period magnesium group showed a significant reduction in the number of patients requesting early postoperative analgesia as well as total fentanyl consumption.

The antinociceptive effects of magnesium are primarily based on the regulation of calcium influx into the cell, as a calcium

antagonism and antagonism of N-methyl-D-aspartate (NMDA) receptor Tanmoy and colleagues¹⁰ evaluated the effect of adding MgSO₄ as adjuvants to epidural Bupivacaine in lower abdominal surgery and reported reduction in time of onset and establishment of epidural block. Whereas, Arcioni and colleagues¹¹ proved that combined intrathecal and epidural MgSO₄ supplementation reduce the postoperative analgesic requirements. Farouk et al¹² found that the continuous epidural magnesium started before anesthesia provided preemptive analgesia, and analgesic sparing effect that improved postoperative analgesia. Also, Bilir and colleagues⁴ showed that the time to first analgesia requirement was slightly longer with significant reduction in fentanyl consumption after starting epidural MgSO₄ infusion postoperatively. Asokumar and colleagues¹³ found that addition of MgSO₄ prolonged the median duration of analgesia after intrathecal drug administration.

On the other hand, Ko and colleagues¹⁴ found that perioperative intravenous administration of magnesium sulfate 50 mg/kg does not reduce postoperative analgesic requirements which could be attributed to the finding that the perioperative intravenous administration of MgSO₄ did not increase CSF magnesium concentration due to inability to cross blood brain barrier.

Nishiyama et al^{17,18,19} reported that epidural midazolam was useful for postoperative pain relief. It was suggested that epidurally administered midazolam exerts its analgesic effects through the α -aminobutyric acid receptors in the spinal cord, particularly in lamina II of the dorsal horn¹⁵ as well as through the opioid receptors. Nishiyama et al²⁰ showed that intrathecally administered midazolam and bupivacaine had synergistic analgesic effects on acute thermal- or inflammatory-induced pain, with decreased behavioral side effects. While, Kumar et al²¹ reported that single-shot caudal coadministration of bupivacaine with midazolam 50 μ g/kg was associated with extended duration of postoperative pain relief in lower abdominal surgery. Whereas, Jaiswal et al²² concluded that epidural midazolam can be useful and safe adjunct to bupivacaine used for epidural analgesia during labor.

In the present study, there were no significant hemodynamic changes between groups. This is in agreement with many authors who used epidural MgSO₄^{4,12,23} and midazolam²⁴ and did not report any hemodynamic or respiratory instability during the observation period.

This study did not record any neurological or epidural drugs related complications postoperatively. Our results are in accord with some of the trials that have previously examined the neurological complications of using epidural MgSO₄^{11,12,23} Moreover, Goodman and colleagues²⁵, found that inadvertent administration of larger doses MgSO₄ (8.7 g and 9.6 g) through epidural catheter did not reveal any neurological side effects.

Regarding epidural midazolam, Nishiyama¹⁹ said that epidural administration of midazolam has a wide safety margin for neurotoxicity of the spinal cord due to the small dose used.

Our results did not reveal any significant difference regarding the sedation score. This is in agreement with Bilir et al⁴ and El-Kerdawy²³ who did not report any case with drowsiness or respiratory depression when using epidural magnesium.

Whereas, De Beer et al²⁶ and Nishiyama et al²⁷ reported that a dose of 50 μ g/kg midazolam appears to be the optimum dose for epidural administration, while many patients fell into complete sleep with no response to verbal command and respiratory depression when they used epidural midazolam 0.075 mg/Kg or 0.01 mg/Kg Moreover, Nishiyama et al^{17,28} reported that when 50 μ g/kg epidural midazolam was used, serum midazolam concentration was less than 200 ng/ml which was considered as the lower limit for sedation by intravenous administration.

In conclusion, co-administration of epidural magnesium provides better intraoperative analgesia as well as analgesic-sparing effect on PCEA consumption without increasing the incidence of side-effects compared to bupivacaine alone or with co-administration of epidural midazolam in patients undergoing total knee replacement. The results of the present investigation suggest that magnesium may be one of the useful adjuvants to epidural analgesia.

Competing Interests

None declared

Author Details

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